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Review

A molecular ensemble in the rER for procollagen maturation☆

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ABSTRACT

Extracellular matrix (ECM) proteins create structural frameworks in tissues such as bone, skin, tendon and cartilage etc. These connective tissues play important roles in the development and homeostasis of organs. Collagen is the most abundant ECM protein and represents one third of all proteins in humans. The biosynthesis of ECM proteins occurs in the rough endoplasmic reticulum (rER). This review describes the current understanding of the biosynthesis and folding of procollagens, which are the precursor molecules of collagens, in the rER. Multiple folding enzymes and molecular chaperones are required for procollagen to establish specific posttranslational modifications, and facilitate folding and transport to the cell surface. Thus, this molecular ensemble in the rER contributes to ECM maturation and to the development and homeostasis of tissues. Mutations in this ensemble are likely candidates for connective tissue disorders. This article is part of a Special Issue entitled: Functional and structural diversity of endoplasmic reticulum.

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1. Introduction

Our structural framework consists of connective tissues such as bone, skin, tendon and cartilage, which play crucial roles in development and homeostasis. We call this framework the extracellular matrix (ECM) and it is composed of structural proteins such as collagens, elastin, fibrillins, laminins and many others. Proper maturation and remodeling of the ECM is required for development and homeostasis. ECM proteins are relatively large molecules compared to general globular proteins. They are primarily biosynthesized in the rough endoplasmic reticulum (rER) [1,2]. The specific biosynthetic processes of many ECM proteins are poorly understood with the exception of type I procollagen biosynthesis. Collagen is the most abundant protein and represents one third of all proteins in humans. Procollagen is the biosynthetic precursor molecule of collagen. Procollagen biosynthesis and quality control take place in the rER. Type I collagen is the major component of various structural connective tissues and its biosynthesis is the best characterized out of the twenty nine types of collagens [1,3]. The quality control of type I procollagen synthesis is also performed in the rER. This overall process can be imagined as a manufacturing process in a factory. Inside a factory, a blueprint is used to produce a commodity by machinery composed of many employees. The procollagen biosynthesis acts in a similar way: procollagen biosynthesis in the rER (factory) requires a large number of proteins that act as posttranslational modifiers, folding enzymes or molecular chaperones (employees).

Collagen has a relatively simple structure. The primary amino acid sequence is composed of Gly-Xaa-Yaa repeats and this polypeptide chain, called the α chain, forms a left-handed polyproline II-like helix. Three α chains align with a one residue stagger into a right-handed superhelix (the triple helix). This structure is highly elongated (300 nm × 1.5 nm for type I collagen) and glycine is packed tightly at the center of the triple helix. All side chains of the Xaa and Yaa position residues are exposed at the molecular surface, which is formed by the three staggered polypeptide chains [1,3,4]. The folding machinery creates type I procollagen in a highly efficient manner—it takes only approximately 10 and 30 min for the translation and folding in the rER and the secretion to ECM, respectively, despite such an elongated shape with numerous posttranslational modifications [5–8]. Procollagen biosynthesis related proteins in the rER interact with one another and form an 'ensemble' to supply quality-controlled collagens to the extracellular space. Improving our understanding of the structure and function of this ensemble will allow us to develop new strategies and approaches for further characterization of collagen structural properties as well as for diagnosis and treatment of collagen-related defects and diseases.

This review focuses on two things: One is that the blueprint of the procollagen folding machinery is drawn with an emphasis on several open questions regarding these processes. Procollagen biosynthesis and secretion in cells is a complicated process and this blueprint is a useful approach to fully understand this process. The other is that different views are provided for the understanding of the procollagen biosynthesis machinery in the rER. The maximum efficiency and effectiveness of this machinery may involve an appropriate rER environment, therefore

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several indirect elements which potentially influence this machinery are shown in this part. Additionally, the correlation between procollagen biosynthesis and the molecular ensemble is discussed from the view point of mutations in this machinery.

2. Complexity of procollagen biosynthesis and secretion in cells

Osteogenesis Imperfecta (OI) is a connective tissue disorder which is characterized by fragile bones with susceptibility to fracture from minimal trauma. OI is usually inherited in an autosomal dominant pattern and distinguished by seven subtypes in humans based on the underlying genetic defects and phenotypic severity [9–11]. 90% of all human OI cases are caused by structural defects in type I collagen due to heterozygous mutations in the type I collagen genes, *COL1A1* or *COL1A2* [9,10,12–14]. A new paradigm emerged in 2006. The report of a human mutation in cartilage associated protein (CRTAP) revealed a recessive form of OI and CRTAP null mice showed osteochondrodysplasia due to severe osteoporosis and decreased osteoid production [15]. CRTAP is a rER resident protein and forms a tight multifunctional complex with prolyl 3-hydroxylase 1 (P3H1) and cyclophilin B (CypB) [15–17]. Since 2006, collagen biosynthesis-related proteins including these three molecules have been identified as recessive genes that cause OI and other collagen related diseases in addition to *COL1A1* and *COL1A2* mutations [8,18–42].

The understanding of procollagen folding and quality control machinery in the rER therefore requires more attention. Why is procollagen biosynthesis so complicated even though a collagen molecule has a rather simple structure? Recently published reviews describe various aspects of these complex processes and identify related proteins [1,43–45]. In this section, unanswered questions particularly regarding biosynthesis and secretion are addressed, including recent new findings. Some of these questions are presently difficult to answer but require clarification in the near future. This section contains two topics: 1) the blueprint of the type I procollagen folding machinery in the rER, and 2) the open questions of type I procollagen biosynthesis and secretion. These parts are likely to also be relevant to the biosynthesis and secretion of all other types of collagens.

2.1. The blueprint of the type I procollagen folding machinery in the rER

Type I procollagen consists of two different polypeptide chains, namely the proα1 and proα2 chain, which are translated from the *COL1A1* and *COL1A2* gene, respectively. These chains are assembled in a ratio of two proα1 to one proα2 chain. Newly synthesized type I procollagen polypeptide chains extend to the luminal part of the rER. Both of the proα1 and proα2 chain have three distinct domains, an amino-terminal noncollagenous domain (N-propeptide and N-telopeptide), a major collagenous region which is composed of 338 Gly-Xaa-Yaa repeats and a carboxyl-terminal noncollagenous domain (C-telopeptide and C-propeptide).

2.1.1. Prior to triple helix formation

The triple helix characterizes the structure of collagen. Before this structure can be formed, multiple steps are required to produce procollagen molecules which function properly in the ECM.

2.1.1.1. Posttranslational modifications on unfolded collagen chains. Hydroxylation occurs co-translationally by three distinct enzyme families: Prolyl 4-hydroxylases (P4Hs), Prolyl 3-hydroxylases (P3Hs) and Lysyl hydroxylases (LHs). These modifications can only occur on unfolded chains (denatured procollagen) (Fig. 1a). These hydroxylases belong to a Fe(II)- and 2-oxoglutarate-dependent dioxygenase family and contain a dioxygenase domain. Ascorbic acid (vitamin C) is essential to return the iron to its oxidized state, especially for prolyl 4-hydroxylases, therefore ascorbic acid is crucial for procollagen biosynthesis [46–48]. P4Hs modify proline to 4-hydroxyproline (4Hyp) in the Yaa position of Gly-Xaa-Yaa repeat and almost all prolines in the Yaa position are 4-hydroxylated in vertebrates. This modification is the most abundant posttranslational modification, which provides thermal stability to the collagen triple helix [49–52].

On the other hand, prolyl 3-hydroxylation is a far less frequent event. In type IV collagen which is reported as a highly 3-hydroxylated collagen, 4-hydroxylation levels reach close to 10% but 3-hydroxyproline (3Hyp) contributes to less than 1% of the amino acid sequence [53–55]. P3Hs hydroxylate proline to 3-hydroxyproline in the Xaa position of a Gly-Xaa-4Hyp sequence, suggesting that 3-hydroxylation occurs after 4-hydroxylation (Fig. 1b) [53–56]. Additionally, the efficiency of this modification is affected by the surrounding sequences of Gly-Xaa-4Hyp [56]. This evidence indicates that substrate preferences may be higher among P3Hs compared to P4Hs. The function of 3Hyp is poorly understood. Mutations or defects in any component of the P3H1/CRTAP/CypB complex result in an overmodification of procollagen during its biosynthesis, which is mainly an increase in glycosylation of the collagen molecule. Improper molecular packing of this overmodified collagen may increase bone fragility, ultimately leading to OI [8,15,19]. 3-Hydroxylation is possibly involved in the quality control of collagen and may contribute to the binding with other ECM molecules such as small leucine-rich proteoglycans and minor collagens like FACITs (*F*ibril-*A*ssociated *C*ollagens with *I*nterrupted *T*riple helices).

LHs target some of the Yaa position lysine residues in Gly-Xaa-Lys tripeptide units of the collagenous domain, as well as sequences in both the N- and C-noncollagenous telopeptide regions (Fig. 1a). This posttranslational modification allows the subsequent glycosylation of hydroxylysine. Hydroxylysines and O-linked glycosylation of hydroxylysines within procollagen molecules ultimately are crucial for the formation of intra- and inter-molecular crosslinks [57–60].

Interestingly, all hydroxylases have three different isoforms in vertebrates, each of which have differences in tissue distribution, substrate preference, additional functions and potential for complex formation with other proteins. P4H exists as a 2:2 stoichiometric heterotetramer. P4H is generally called the α subunit and exists as three isoforms, namely α(I), α(II) and α(III). All α subunits require a β subunit, known as Protein Disulfide Isomerase (PDI), to form an enzymatically active complex [61]. PDI is a rER resident oxidoreductase and a molecular chaperone. The PDI β subunit is required to maintain the solubility of the P4H α subunit and to keep the complex within the rER [62]. This complex intermittently interacts with unfolded procollagen chains and may keep them retained inside the cell when hydroxylation is inhibited [63]. The three isoforms, $\alpha(I)_2\beta_2$, $\alpha(II)_2\beta_2$ and $\alpha(III)_2\beta_2$ show different expression levels and patterns [64–68]. The P4H $\alpha(I)_2\beta_2$ is the major expressed form [65]. The α(I) subunit null mice exhibit embryonic lethality and basement membrane defects caused by the loss of type IV collagen assembly [66]. The P4H $\alpha(II)_2\beta_2$ is found in chondrocytes and capillary endothelial cells [65]. The P4H $\alpha(III)_2\beta_2$ has lower expression levels than α(I) and α(II) [68]. Similarly, it has been shown by northern blot analysis that P3H1, P3H2 and P3H3 have distinct tissue distributions [69]. P3H1 is mainly expressed in fibrillar collagen rich tissues, whereas P3H2 is located in basement membrane rich tissues such as kidney [56,69]. P3H3 mRNA is abundant in the brain but also shows a more general expression pattern [69].

P3H1 is the best characterized protein compared to the other isoforms. P3H1 forms a tight complex with CRTAP and CypB in a 1:1:1 stoichiometry and this complex performs multifunctional roles during procollagen biosynthesis such as general molecular chaperone, prolyl hydroxylase and peptidyl–prolyl *cis–trans* isomerase (PPIase) [15–17]. The absence of any component of the P3H1/CRTAP/CypB complex leads to OI [15,18–27]. Knock-out mice of P3H2 show embryonic lethality (Pokidysheva, E. unpublished data), and human mutation in P3H2 results in autosomal-recessive high-grade axial myopia [70]. Very little is known about P3H3. It has been reported as being epigenetically silenced in breast cancer together with P3H2 [71], and knock-out mice of P3H3 are viable (Ishikawa, Y. unpublished data).

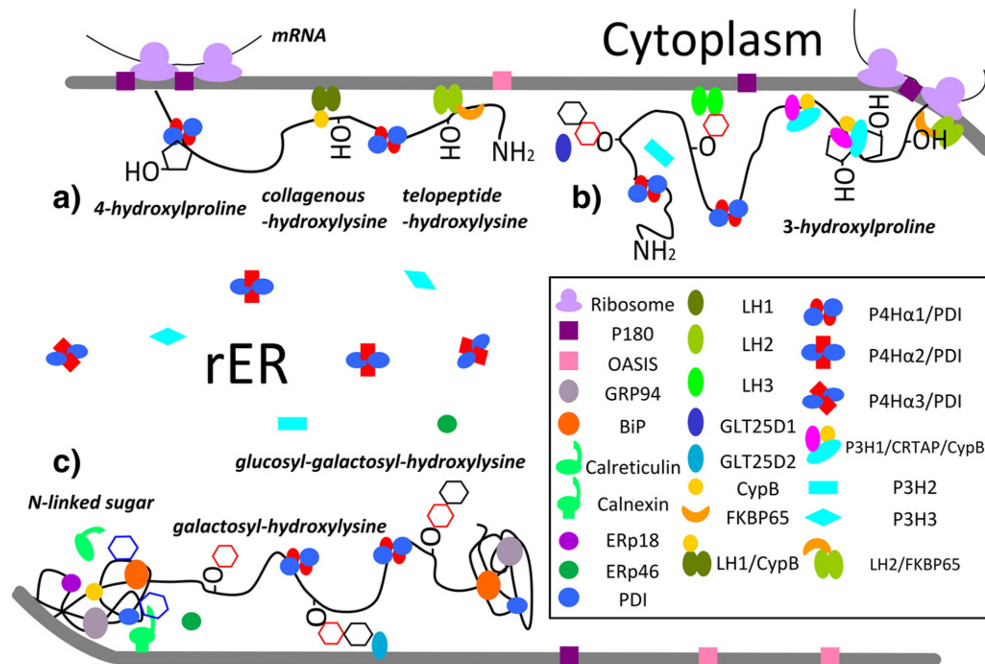

Fig. 1. Schematic illustration of the posttranslational modifications during biosynthesis of type I procollagen before triple helix formation. The newly synthesized proα chain extends to the luminal part of rER. a) Prolyl 4-hydroxylation and lysyl hydroxylation occur on the proα chain. b) The proα chain is prolyl 3-hydroxylated after prolyl 4-hydroxylation. c) Some of the hydroxylysine residues are glycosylated to galactosyl-hydroxylysine and glucosyl-galactosyl-hydroxylysine.

LHs have three isoforms LH1, LH2 and LH3. LH2 has two splice variants, the shorter form LH2a and the longer form LH2b [72]. Moreover, LHs have been suggested to form homodimers and be associated with the rER membrane [73–77]. LH3 possesses not only lysyl hydroxylase activity but also hydroxylysyl galactosyltransferase and galactosyl hydroxylysyl glucosyltransferase activities [78–82] although the galactosyltransferase activity is marginal [83]. LHs also show different tissue distributions which vary during the course of mouse development [84–86]. LH1 is highly expressed at the embryonic developmental stage and the other two LHs are expressed throughout embryonic and adult development. LH3 has a general tissue distribution whereas LH2 shows more specific localization in muscles and heart [84]. Additionally, the shorter form LH2a has a more restricted distribution compared to the longer form LH2b in humans [72]. The LH1 and LH3 null mice showed early postnatal death and embryonic lethality, respectively [87,88]. LH1 null mice demonstrated fibrillar collagen tissue defects such as altered aorta and skin morphology. On the other hand, LH3 null mice showed affected basement membranes caused by premature aggregation of type IV collagen. The loss of both functions of LH3 must be crucial for the basement membrane quality control. Mutations in LH2 result in Bruck syndrome, an autosomal recessive connective tissue disorder, which affects a crosslink formation due to the lack of lysyl hydroxylations in the telopeptide [89,90].

The prolyl 3-hydroxylation is likely to occur following the prolyl 4-hydroxylation. On the other hand, the temporal order of prolyl 4-hydroxylation and lysyl hydroxylation is not clear. The luminal location of P4Hs and the membrane association of LHs might be important for efficient posttranslational modifications (Fig. 1a and b), however further studies are required to shed more light on temporal and spatial aspects of the procollagen hydroxylations. The major conclusion is that these three different hydroxylation events are crucial for the formation of a functional triple helical structure.

2.1.1.2. O-linked sugar modification of hydroxylysine residues. Some hydroxylysine residues are further modified with two different carbohydrates, β-galactose and α-glucose. These modifications are catalyzed by three transferases, GLT25D1 (glycosyltransferase 25 domain containing 1), GLT25D2 [83,91,92] and LH3 (Fig. 1b and c) [79,80]. GLT25D1 and GLT25D2 are a soluble rER luminal and a transmembrane protein, respectively. They function as galactosyltransferases [83]. LH3 acts as both a galactosyltransferase and a glucosyltransferase, but the galactosyltransferase activity of LH3 is marginal [78,80,82,83]. The studies of LH3 [81,88] suggests that the attachment of O-linked sugars are biologically important for the (pro)collagen molecule, nevertheless its function is still unknown. In vitro enzyme activity studies suggest that this sugar attachment takes place on unfolded procollagen chains [78,80,83], however there is no clear evidence to support this hypothesis in vivo. Further studies are required to better understand this procollagen maturation process.

2.1.1.3. N- and C-propeptide folding and chain selection. Folding of both N- and C-propeptides, as well as the chain selection through the C-propeptides, occurs before the initiation of the triple helix formation. During the folding process of the propeptides, especially of the C-propeptides, general rER resident molecular chaperones and folding enzymes (BiP/Grp78, Grp94, PDI, calreticulin, calnexin and CypB) are active players (Fig. 1c) [4,26,93–97]. Type I procollagen folding is suggested to take place with the C-propeptides closely associated with the rER membrane [98]. The C-propeptide attaches to it directly or indirectly (Fig. 1c). This seems reasonable because two dimensional diffusion on the rER membrane leads to a higher probability of three different chains assembling together than a trimolecular reaction in three dimensional space of the rER lumen. Disulfide bond formation, peptidyl–prolyl *cis*–*trans* isomerization and N-linked glycosylation are cooperatively involved in the folding of the C-propeptide with support from a general chaperone [39,40].

Three properly folded C-propeptides assemble and form the nucleus for the triple helix formation [99]. PDI has been reported as an important enzyme/chaperone for proper chain selection because the C-propeptide forms not only intrachain disulfide bonds but also interchain disulfide bonds [95–97]. Recently, the crystal structure of the C-propeptide of type III procollagen was solved, thereby answering the long standing question about the disulfide bonding of eight

cysteines [100]. PDI has been called a major disulfide catalyst during procollagen biosynthesis. However, there are more than 20 oxidoreductases (PDI family proteins) that reside in the rER [101]. ERp18 and ERp46 might also be involved in the type III collagen C-propeptide and type IV and VI procollagen folding [102]. The conclusion here is that the folding of collagen propeptides (at least for fibrillar collagens) is a crucial prerequisite for the next step, chain propagation. The C-propeptides of the α1 and α2 chain of type I collagen contain a single N-linked glycosylation site. This Asn-Ile-Thr sequence is highly conserved among fibrillar procollagens (type I, II, III, V and XI) [103,104]. Mutagenesis studies of the α1 chain of type I procollagen showed that unglycosylated α1 chains did not alter assembly, folding and secretion. The sensitivity against C-propeptidase was slightly decreased. This N-linked glycosylation may have a function for the maturation of type I procollagen secreted from the rER [105].

2.1.2. Triple helix formation and chain maturation

After completion of the chain selection through the C-propeptides, triple helix formation proceeds from the carboxyl-terminal nucleus toward the amino-terminal end in a zipper-like fashion (Fig. 2a) [106,107]. The collagenous sequence frequently contains proline residues and the Yaa-position in the Gly-Xaa-Yaa repeats are often occupied by 4-hydroxyproline. The imino acid proline is unique among the amino acids because it has two different peptide bond conformations, the *cis* and *trans* forms, which have similar energies, however all peptide bonds in the triple helix need to be in the *trans* conformation. While the initial peptide bond formed on the ribosome is likely *trans*, *cis* bond formation does occur and was observed in nascent α-chains (unfolded chain) of type I procollagen [108]. This suggests that the unfolded procollagen chains have enough time to isomerize prolines to their *cis*–*trans* equilibrium state. The rate-limiting step in triple helix formation is the *cis*–*trans* isomerization of prolyl peptide bonds and prevention of this isomerization results in a decreased rate of procollagen folding [7,106,107,109–111].

Peptidyl prolyl *cis*–*trans* isomerases (PPIase) catalyze the conformational change from *cis* to *trans* prolyl peptide bonds. Three PPIase families exist in the cell: cyclophilins, FK506 binding proteins (FKBP) and parvulins. There are six FKBP family members and one member of the cyclophilin family present in the rER [43,112]. Cyclophilin B (CypB) has been proposed as a major triple helical catalyst [7,110,111] and forms complexes with many collagen related proteins in the rER such as PDI, P3H1/CRTAP, calreticulin/calnexin, Hsp47 and LH1 [17,42,113–115]. CypB forms a tight complex with P3H1/CRTAP, but free CypB was also shown to exist in sedimentation experiments of gelatin binding rER proteins [15]. Equilibrium dissociation constants (*Kd*) were in the μM range for PDI and the P-domain of calreticulin [42,115]. These weak interaction networks might be widespread in the rER and further studies are required to understand the function of CypB in these complexes.

FKBP13, 19, 22, 23, 60 and 65 are rER resident FKBP family proteins. FKBP65 has been characterized as a procollagen chaperone and as a possible elastin associated protein. FKBP65 was initially proposed to be a tropoelastin chaperone [116] and later was identified as a procollagen chaperone during biosynthesis and maturation [117,118]. FKBP65 consists of four FKBP domains, similar to FKBP13, and possesses a rER retention signal. The PPIase activity of FKBP65 was marginally inhibited by FK506, which is an inhibitor against the PPIase activity of FKBPs, and did not exhibit significant enhancement of type III collagen refolding in vitro [117]. However, FKBP65 functioned as a molecular chaperone for type I and III collagen [118]. This protein prevents fibril formation of type I collagen and provides an increase in the thermal stability of type I and III collagen. These results suggest that FKBP65 interacts with the triple helical structure and avoids premature association between procollagen molecules in vivo.

Mutations of either *PPIB* (gene for CypB) or *FKBP10* (gene for FKBP65) lead to OI and mutations in *FKBP10* are also related to Bruck syndrome [18,24,32,33,37,38,119]. A recent publication suggests that FKBP65 might be involved in the activity of LH2 to hydroxylate lysines in the telopeptide region [37]. Recently it was shown that human mutations in *FKBP14* (gene for FKBP22) cause the kyphoscoliotic type of Ehlers–Danlos syndrome and myopathy [120,121]. This type of Ehlers–Danlos syndrome is characterized by severe muscle hypotonia at birth, progressive kyphoscoliosis, marked skin hyperelasticity with widened atrophic scars, and joint hypermobility. Deficiency in LH1 (PLOD1) also results in this type of Ehlers–Danlos syndrome [122–124]. The FKBP22 protein is composed of one FKBP domain, two calcium binding EF-hand domains and a rER retention signal at the

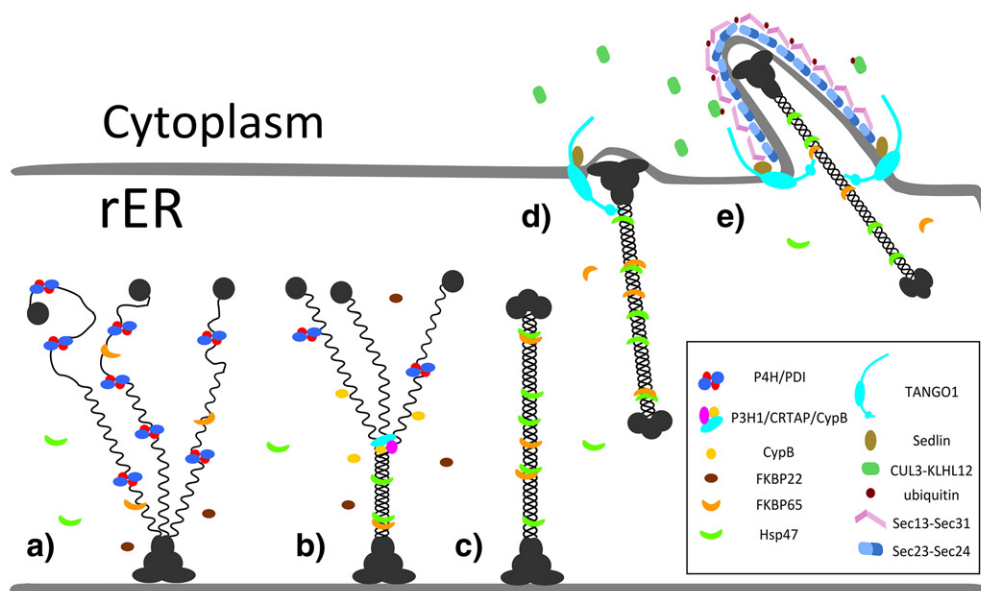

Fig. 2. Schematic illustration of the triple helix and COPII vesicle formation of type I procollagen. a) The three posttranslationally modified α chains assemble near/at the rER membrane. b) The PPIases catalyze triple helix formation and c) the triple helix is stabilized by the molecular chaperones. d) TANGO1 initiates the procollagen specific COPII vesicle and e) the cytoplasmic proteins elongate this special COPII vesicle.

carboxyl terminal end [112]. Bacterial FKBP22 was studied by several groups [125–127], however the function of human FKBP22 is not well understood.

During the zipper-like triple helix formation of procollagen, there is a junction between folded and unfolded chains. This junction is likely to be unstable. The P3H1/CRTAP/CypB complex interacts with both folded and unfolded chains and kinetic data showed that the dissociation rate constant (*kd*) of this complex was faster than that of the collagen specific molecular chaperone Hsp47 against folded type I collagen [17]. The P3H1/CRTAP/CypB complex is therefore proposed to be a molecular chaperone for this junction until Hsp47 and/or FKBP65 further stabilize the newly formed triple helix (Fig. 2b and c).

Hsp47 is called a collagen specific molecular chaperone and is only upregulated by heat shock stress in the rER [128,129]. Hsp47 belongs to the serine protease inhibitor (SERPIN) superfamily but does not possess protease inhibitory activity [130]. This protein recognizes the triple helical form of collagen [131,132] and traverses from the rER to the Golgi with procollagen [133]. Once Hsp47 reaches the Golgi, it dissociates from procollagen and is thought to be captured by its rER retention signal and recycled to the rER via COPI vesicles in a pH dependent manner [134,135]. Recently the binding region of Hsp47 to collagen was determined by the crystal structure and NMR measurements with collagen model peptides [136,137]. Hsp47 was shown to directly bind to folded type I, II, III, IV and V collagens by surface plasmon resonance analysis [138]. The strongest affinity was found for sequences with Thr/Pro-Gly-Xaa-Arg-Gly and at least one of these sequences is present in all twenty nine types of collagens [139–141]. Hsp47 knock-out mice show that embryonic lethality and mutations in Hsp47 lead to OI in humans and dachshunds [29,30,142]. Therefore Hsp47 plays an important role in the quality control of folded procollagens. If the cell recognizes aggregating misfolded collagens, the unfolding protein response (UPR) is activated to eliminate them.

The ER associated degradation (ERAD) pathway has been shown to be activated by procollagen aggregation of unfolded collagen chains, whereas triple helical procollagen aggregates were taken up by the autophagy mediated lysosomal degradation system [143]. Thus, it is evident that the rER closely monitors procollagen structures for cell protection, suggesting that procollagen quality control is highly sophisticated. In conclusion, triple helical acceleration by PPIases and maturation by triple helical chaperones are cooperative reactions ensuring that the rER retains appropriate rates of folding.

2.1.3. Secretion—special COPII vesicle formation at ER exit sites

In mammalian cells, proteins synthesized in the rER traverse to the Golgi apparatus, continuing through to the *trans*-Golgi network (TGN), and finally to the ECM. They are packed into transport vesicles to move from one compartment to another. The first step is from the rER to the Golgi and these vesicles are called COPII vesicles [144]. COPII vesicles are approximately 60–80 nm diameters in size, and move from the ER exit sites to the Golgi with loaded cargo molecules [145,146]. Once at the *cis*-Golgi several models have been suggested by which proteins can pass through the Golgi to TGN. These include 'cisternal maturation', 'vesicular transport' and 'rapid partitioning' [147–150]. Folded procollagen is highly elongated (300 nm × 1.5 nm for type I collagen) and does not fit into classical COPII vesicles, thus a special vesicle formation for collagen has been suggested [151,152].

Recently, a knockout mouse study of the transmembrane protein TANGO1 showed that the lack of TANGO1 resulted in a defect in secretion of various types of collagens, such as type I, II, III, IV, VII and IX, and a delay of chondrocyte and bone maturation [153]. Cell biology studies have suggested that the SH3 domain, which is located at the N-terminus of TANGO1 and resides inside the rER, recognizes type VII collagen and assists in the formation of collagen-like COPII vesicles [154,155]. Special cargo formation may be triggered by the binding of the SH3 domain of TANGO1 to procollagen molecules (Fig. 2d). The cytoplasmic domain of TANGO1 then recruits Sec13/31 and Sec23/24 to form extended COPII vesicles [156–159]. The regulation of these Sec proteins has been proposed to be an important factor for the formation of these extended COPII vesicles for procollagen transport (Fig. 2e) [160–162]. The cytoplasmic protein complex CUL3–KLHL12 regulates the size of expanding COPII vesicles by monoubiquitylation of Sec31 in mouse ES cells (Fig. 2e) [163]. The Sec13/sec31 are also suggested to form a suitably large cargo tubule for procollagen transport by in vitro experiments [164], but this mechanism of regulation is unknown. The ubiquitylation of Sec31 might be essential for procollagen trafficking to regulate and create large cargo carriers.

Another important protein seems to be Sedlin, which controls the GTPase Sar1 cycle and affects procollagen trafficking at the rER exit site [165]. Results show that a knockdown of Sedlin specifically affects procollagen secretion while total protein secretion was not significantly changed [165]. A suggested model is that TANGO1 recruits Sedlin, which promotes an efficient Sar1 cycle (Fig. 2e). Sar1 recruits the COPII coat proteins at the rER exit site [166]. These recent studies lead to the conclusion that procollagen transport requires protein–protein interactions and signaling between the rER and the cytoplasm to form special cargo vesicles.

The procollagen molecules are then finally secreted into ECM. It is unclear at what stages a pre-fibril assembly of these molecules occurs. It is likely that this assembly occurs in the post Golgi compartment [151,167], but that this assembly is actively inhibited by Hsp47 and other chaperones in the rER [17,118,135]. It is clear that for type VI collagen the assembly into tetramers is an intracellular event [168]. For fibrillar collagens, the oxidation of lysine residues by lysyl oxidases in preparation for cross linking and proteolytic cleavage of the propeptides for efficient fibril formation are also required. These processes still include various black boxes and further characterizations of proteins that assist in the maturation of procollagen are necessary.

2.2. Open questions regarding procollagen biosynthesis

Collagen is the most abundant protein in the human body and therefore cells must use a large amount of energy for procollagen biosynthesis. Although collagen has a relatively simple structure, procollagen/collagen biosynthesis needs many rER resident proteins. This suggests that cells must consume additional energy to maintain these collagen related proteins. Additionally, the rER has a high protein concentration whereby the total protein concentration in the compartment can reach up to 100 mg/ml [169]. At least fifteen rER resident proteins are involved in this complex protein synthesis. Their ensemble is closely organized and highly effective in managing this molecular crowding. The studies of the functions of rER proteins and protein–protein interaction networks are essential aspects for the understanding of this complex event.

2.2.1. Maturation of proline: combination of modification and isomerization

Proline and glycine are the most common amino acids in the collagenous sequence. The posttranslational modifications of proline residues have an important contribution to procollagen biosynthesis. As described earlier, three different prolines exist in the collagenous sequence: proline, 4-hydroxyproline and 3-hydroxyproline. The rate-limiting step in triple helix formation is the *cis*–*trans* isomerization of peptide bonds of proline residues. PPIases catalyze the conformational change from the *cis* to *trans* peptide bond. There is one cyclophilin and six FKBP family proteins in the rER. Therefore each proline in the collagenous sequence has theoretically three variants and eight potential isomerization possibilities (seven PPIases and uncatalyzed isomerization). There is no information about substrate specificities or preferences between proline types and PPIases. It is likely that preferences of these PPIases exist and this would provide new insight into the process of procollagen biosynthesis.

2.2.2. Is CypB the major physiological catalyst during triple helix formation?

Early in vitro [110] and fibroblast studies with cyclosporin A which is an inhibitor of the PPIase activity of cyclophilins [7,111] showed a clear catalytic effect due to inactivation of CypB activity. Recently, the physiological role of CypB in collagen folding became somewhat controversial. In vivo studies with CypB null mice [21] and CypB null cells from recessive OI patients [18,26] questioned the in vitro conclusion. In the null fibroblast experiments, the authors concluded that the rate of folding must not be affected because the collagen overmodifications were not observed [18]. Additionally in the other study with null fibroblast experiments the hypothesis was raised that CypB is more important for the rate of trimer formation [26]. A likely resolution of the controversy against these null fibroblast experiments was presented from studies of a mutation in the American Quarter Horse [42]. A homozygous mutation of a single amino acid in horse CypB shows the same PPIase activity compared to wild-type CypB in vitro. However, the rate of folding in horse fibroblasts is delayed without the presence of overmodified collagens. These results were caused by an aberrant CypB–LH1 interaction [42]. Mutations in CypB therefore have two effects: it reduces the activity of LH1, and it also delays the rate of folding of the collagen triple helix. When FKBPs are inhibited by FK506 in fibroblasts, only a minor delay in the rate of folding of type I collagen is observed [7]. The caveat is that FKBP65 is only partially inhibited by FK506, but given that FKBP65 is still present in CypB null fibroblasts, CypB is the major PPIase for collagen triple helix formation considered with fibroblast studies [7,111]. Seven PPIases may partially compensate each other for the lack of PPIase activity to maintain the rER homeostasis during procollagen folding. CypB is not only the major PPIase for collagen triple helix formation, but it is also involved in complex formation with other collagen related molecules [17,42,113–115]. Further studies are required to define which function of CypB is crucial during procollagen biosynthesis.

2.2.3. Is there a different posttranslational modification machinery in fibrillar collagen producing cells?

Type I collagen is the most abundant type out of twenty-nine types of collagen. It is present in fibrillar rich tissues such as tendon, skin and bone. Differences in posttranslational modifications of pepsinized type I collagen extracted from various tissues are observed by amino acid analysis and mass spectrometry in spite of the same primary amino acid sequences [8,42,170]. The amount of hydroxylysine in skin was determined to be lower than in tendon. O-glycosylation was observed to be lowest in bone compared to skin and tendon. Mass spectrometry also showed the tissue specific distribution and extent of prolyl 3-hydroxylation. Therefore collagens potentially have different posttranslational profiles dependent on the source of tissue.

Most of the Yaa position lysine residues in Gly-Xaa-Yaa in type V, VI and X collagens are hydroxylated and glycosylated, while only a few residues are glycosylated in type I and III collagens [171–174]. Each tissue requires a specific property of type I collagen and the biosynthesis may adjust for the required effect. The main component of tendon is type I collagen, but skin contains not only type I collagen but also type III, V and IV collagens. For the strength required in bone, mineralization of the collagen fibrils occurs. While the primary amino acid sequence in collagen is composed of Gly-Xaa-Yaa repeats, the repertoire of posttranslational modifications allows for the generation of tissue specific properties of collagens. This can be accomplished by cell specific expression of certain collagen modifying proteins. For example, mRNA of P3H2 is abundant in basement membrane rich organs such as kidney, suggesting that P3H2 may be involved in type IV procollagen biosynthesis and quality control [56,69]. LH1 is highly expressed at later embryogenesis stages thereby LH1 is possibly more important for fibrillar collagens given the fact that fibrillar collagen rich tissues develop rapidly at this stage [72].

2.2.4. Can collagens be expressed recombinantly in vitro?

If human collagens could be recombinantly expressed and purified on a large scale, there is great potential for these molecules to be applied in the field of medicine, for example, material for tissue engineering and growth scaffold for stem cells and iPS cells. Various approaches have been used to express recombinant procollagens in several cell types since the early 90s (see review and the most recent studies [175–178]). There are two major concepts for these studies: a large scale preparation of fibrillar collagens and a characterization of minor types of collagens. The former concept is for medical or biomaterial applications and the latter is for understanding their functions because tissue extraction is extremely difficult and the biological relevance of minor types of collagens is still poorly understood. For example, the amount of type VII collagen is less than 0.001% in human skin [179].

Two major expression systems were used in these studies: mammalian cell cultures and insect cell expression systems [175]. Human Embryonic Kidney (HEK) 293 cells have been widely used to express ECM molecules because ECM proteins including collagens show low intrinsic expression in this mammalian cell [180]. However, almost all cases require the co-expression of the P4H α and β subunits to obtain proper secretion, thermal stability and sufficient amounts of recombinant collagens. Moreover, incorrect chain selection and small amounts of secreted collagen were reported when heterotrimeric collagens were expressed [178,181,182]. In cancer cells, type I collagen is observed as $\alpha1(I)_3$ homotrimers instead of $\alpha1(I)_2\alpha2(I)$ heterotrimers [183,184]. As mentioned, certain collagen modifying proteins show specific expression patterns in cells thereby these distributions may allow collagens to generate tissue specific properties. The content of lysyl hydroxylation and glycosylation was different in collagens expressed in HEK 293 cells compared to those extracted from tissue. The HEK 293 cells also have a low expression level of Hsp47 [185].

Extractable collagens from tissue permit the evaluation of the quality of recombinant collagens, but given the difficulty of extraction of minor types of collagens, the recombinant products are hard to evaluate. To overcome these issues, further technical innovations and accumulation of information about the correlation among collagen types, cell types, and collagen biosynthesis related protein expressions are required.

The biosynthesis of procollagens is a complicated process and a large number of proteins are involved in this process. Despite significant progress many questions remain, but the answers may contain a strategy to develop medical or biomaterial applications and to treat collagen related diseases.

3. Further characterization of the procollagen biosynthesis machinery

Protein biosynthesis in the rER with maximum efficiency and effectiveness may require at least two factors: 1) that the rER is structurally and functionally optimized (indirect effects) and 2) that the biosynthesis machinery performs properly (direct effects). In this section, we show recent studies of the rER involved in procollagen biosynthesis machinery.

3.1. The role of the rER environment on procollagen biosynthesis

Procollagen biosynthesis occurs in the rER. This compartment has a defined environment: a certain pH, calcium content, redox potential and membrane organization. Here we consider how this environment affects procollagen biosynthesis and secretion.

3.1.1. Organization of rER membrane proteins

Procollagen folding is suggested to take place at the rER membrane through either direct or indirect interactions [98], so the membrane organization is important for this process. P180 is a rER membrane protein

and highly expressed in secretory tissues [186]. It was originally reported as a ribosome binding receptor [187] and more recently reported to regulate polysome assembly on the rER membrane [188]. The overexpression of P180 showed enhancement of protein secretion including procollagen whereas the suppression of P180 negatively affected procollagen biosynthesis and secretion [189,190]. Interestingly, large ECM proteins like fibronectin are also affected by the depletion of P180. In contrast, smaller ECM proteins such as TIMP-1 and MMP2 were secreted normally [189,190]. Two transmembrane proteins were shown to be involved in type I procollagen biosynthesis and secretion during bone formation. Osteopotentia is a rER membrane protein which controls postnatal osteoblast maturation [191]. The lack of osteopotentia results in the disruption of the rER ultrastructure and a defect in type I procollagen biosynthesis. This also leads to a failure of bone remodeling [191].

OASIS containing a transmembrane region is a member of the CREB/ATF family [192]. This protein is highly expressed in osteoblasts. OASIS null mice showed a decreased amount of type I collagen in their bone matrix. Knockout osteoblast cells showed an abnormally elongated shape of the rER and loss of type I collagen fibrils in culture [193]. Each of these three membrane proteins provides specific functions: P180 is involved in polysome assembly, OASIS is identified as an ER stress inducer and osteopotentia is involved in osteoblast maturation. These proteins may not interact with procollagen directly but they do affect the biosynthesis and secretion process. Nevertheless, all defects in these transmembrane proteins lead to the failure of these processes and show abnormal rER shapes. This suggests that membrane organization is an essential parameter for proper procollagen biosynthesis and secretion.

3.1.2. Calcium content in the rER

Many molecular chaperones and folding enzymes such as BiP/Grp78, Grp94, PDI calreticulin and calnexin interact with calcium. Such calcium binding by multiple resident rER proteins is proposed to make the rER a high calcium storage compartment in the eukaryotic cell [43,194]. FKBP65 contains two calcium binding EF-hand motifs and calcium binding is known to provide stability for FKBP65 [195]. The crystal structure of the C-propeptide of type III procollagen shows bound calcium suggesting that calcium is required for its folding process [100]. The mineralization of collagen fibrils with calcium occurs in the matrix to provide strength to collagen fibrils in bone. The calcium concentration and/or flow in the rER might be distorted and indirectly affect procollagen maturation.

Two trimeric intracellular cation-selective (TRIC) channel subtypes, namely TRIC-A and TRIC-B, are known to act as intracellular calcium modulators. These proteins are located in the sarco/endoplasmic reticulum, containing three putative membrane-spanning segments to form a bullet-shaped homo-trimeric assembly [196,197]. Neonatal lethality is observed in TRIC-B knock-out mice [196,197]. TRIC-B knock-out cells showed compromised calcium handling [196], and just recently it was shown that human mutations in *TMEM38B* (gene for TRIC-B) lead to autosomal recessive OI [198]. This is a good example that either membrane or calcium defects affect procollagen biosynthesis.

3.1.3. Redox condition in the rER

More than 20 PDI protein family members have been reported to exist in the rER in addition to oxidases including Ero1α. PDI, a major oxidoreductase among the PDI family proteins, forms a heterotetramer with P4H, which is crucial during procollagen biosynthesis (see above). There are redox networks and/or cascades which comprise multiple and multistep electron transfer pathways for oxidation, isomerization and reduction to maintain disulfide bonds of nascent proteins in the rER [199–202]. Several proteins involved in procollagen biosynthesis, as well as procollagen itself, may also be part of these networks.

The redox environment in the rER is oxidative compared with that of the cytosol, which promotes the formation of disulfide bonds in the newly synthesized polypeptides for correct folding [203]. As previously described, hydroxylation of proline residues at the third position of Gly-Xaa-Yaa sequences of procollagen by P4H is a prerequisite for triple helix formation. This reaction requires oxygen, α-ketoglutarate, iron (II) and ascorbic acid. Molecular oxygen and α-ketoglutarate contribute in the formation of a highly reactive Fe(IV) = O which mediates hydroxylation of proline residue. Ascorbic acid plays a crucial role as an important co-factor to reduce the inactive iron (III) state to the active iron (II) state in the dioxygenase domains of P4H [48,204–206]. In addition to the prolyl hydroxylation, the cysteines in the C-propeptides form intra/interchain disulfides between proα1- and proα2-polypeptide chains before triple helix formation.

This oxidation of cysteines is mediated by oxidative relays of electrons such as between Ero1α and PDI. Recently it was shown that combined loss-of-function mutations in three rER thiol oxidases affected the intracellular procollagen maturation [207]. The content of 4Hyp in the tissue was decreased with abnormal connective tissue by the rER thiol oxidases ERO1α, ERO1β and PRDX4 loss-of-function mutated in mice. The authors concluded these defects were caused by depletion of ascorbic acid and a noncanonical form of scurvy due to thiol oxidase deficiency [207]. Thus the regulation and maintenance of the redox environment is essential for procollagen biosynthesis.

Procollagen biosynthesis is basically performed with the help of a wide variety of proteins as described. However, these proteins and procollagen itself are influenced by the environment of the rER. The rER environment will affect the folding of not only procollagen but also that of procollagen related proteins. Defects that lead to a change in the folding environment could lead to changes in the biosynthesis of procollagens. It is therefore likely that mutations in these seemingly unrelated proteins could cause diseases generally associated with ECM proteins.

3.2. Disruption of the procollagen biosynthesis

As we described above, the biosynthesis of procollagen is a complicated process and an ensemble of proteins is involved in this process. A defective product can be produced by cells due to the errors in the blueprint for the procollagen molecules themselves or the errors in the blueprint of the machinery.

3.2.1. Mutations in procollages genes

Collagen genes have been identified as causes of a wide variety of connective tissue disorders affecting almost all tissues and organs [2,208,209]. Mutations in the genes of collagens can lead to nonsense mediated mRNA decay, reducing the amount of collagens being made, or expression of faulty collagen chains. The procollagen folding machinery tries to deal with the faulty chains and a large number of publications describe adverse effects of such mutations [93,210–220]. The cell has several possibilities to deal with such faulty collagen chains, depending on the collagen and the nature of the mutation. Some of these mutated chains are secreted into the ECM with structural defects that can lead to an altered structure of the matrix. Others activate the unfolded protein response (UPR) by the accumulation of misfolded proteins inside the rER. In cases where this ER stress response fails, proteins need to be degraded [2,221]. From studies with Hsp47 it became clear that cells deal with these faulty procollagen molecules using two strategies. If the faulty collagen molecules accumulate before the formation of the triple helix, the ER associated degradation (ERAD) pathway is used for elimination from the rER. On the other hand, once the triple helix is formed, but the folded procollagens accumulate in the rER, procollagens are taken up by the autophagy mediated lysosomal degradation system [143]. As we described in the section of the rER environment, there will be additional molecules/machineries in the rER that assist the procollagen folding machinery in cases of malfunction.

3.2.2. Mutations in genes encoding proteins of the procollagen folding machinery

Each protein of the folding machinery has a certain function in this molecular ensemble during biosynthesis and secretion. The absence of one member of this ensemble leads to a malfunction of the machinery. Results from studies of recessive Osteogenesis Imperfecta (OI) illustrate these malfunctions. Five genes *LEPRE1*, *CRTAP*, *PPIB*, *FKBP10* and *SERPINH1* have been reported as recessive OI genes which encode for proteins in the ensemble [8,18–42]. The absence of P3H1 and CRTAP leads to similar changes in the type I collagen molecules: there is a lack of 3 hydroxylation at Pro986 of the α1 chain and an increase in glycosylation of both collagen chains. The type I procollagen shows a slower rate of folding and secretion and a slightly higher melting temperature [19,20,22,23,25,27,28,34]. The absence of CypB has already been discussed in Section 2.2.2. The absence of FKBP65 and Hsp47 has a different effect on type I procollagen. A lower thermal stability is observed with no changes in 3-hydroxylation or glycosylation. However, a slower rate of secretion was found [30,31,35]. One explanation for these differences is that the P3H1/CRTAP/CypB complex is involved in processes on the unfolded procollagen chains, whereas Hsp47 and FKBP65 preferentially interact with triple helical procollagen. Recently a human mutation in *FKBP14* (gene for FKBP22) was identified as a causal gene for Ehlers–Danlos syndrome [120]. Human mutations in type III and V collagen genes result in Ehlers–Danlos syndrome [2,209]. The specific function of FKBP22 in the rER and its relation to procollagen biosynthesis is still unclear, but it seems likely that this protein is involved in the biosynthesis of type III and/or V collagen instead of type I collagen. Further studies are required to verify that collagen type specific proteins belong to the ensemble.

It is interesting to note that the phenotype of recessive OI is established in humans, and that null mouse models of these proteins show disturbances in other tissues as well [222–231].

3.2.3. Why do certain mutations lead to Osteogensis Imperfecta, Bruck syndrome or Ehlers–Danlos syndrome?

In the previous section recessive OI was used to correlate the absence of proteins of the folding machinery with defects in the procollagen molecule. There are defects in the folding machinery that leads to other related connective tissue disorders, Bruck syndrome and Ehlers–Danlos syndrome. These molecules are lysylhydroxylases 1 and 2 (LH1 and LH2). LH1 modifies lysine residues in the triple helical region and LH2 modifies lysine residues in the telopeptides. A deficiency in LH1 (*PLOD1*) was shown to result in Ehlers–Danlos syndrome [122–124]. On the other hand, mutation in LH2 leads to Bruck syndrome [89,90]. This suggests that the difference of a missing hydroxylysine in the triple helix or telopeptides defines the direction of these diseases. FKBP65 may interact with LH2 and a mutation in FKBP65 also causes Bruck syndrome [33,37,39,119]. This is another indication that the absence of functionally interacting proteins may cause related but different phenotypes, depending on what part of the machinery is affected.

The genetics of recessive OI and other diseases have provided important clues to additional components of this complex biosynthesis machinery. These include the transcription factor *OSX* (encodes Osterix) [232], the collagen binding protein *SERPINF1* (encodes pigment epithelium-derived factor) [233,234], the osteoblast-specific small transmembrane protein *IFITM5* [235–237], the cation channel *TMEM38B* [198] and the procollagen type I C-propeptidase *BMP1* [238]. The exact mechanisms why the absence of these molecules leads to OI need to be established. However it is remarkable that in humans most of these mutations result in a bone phenotype, given the assumption that the collagen folding machinery is used by all types of collagens.

4. Conclusion

ECM maturation is essential for the development and homeostasis of tissues. Collagen plays a crucial role in this context. Procollagen/collagen biosynthesis is a complicated process, and numerous folding enzymes and molecular chaperones are involved despite the relatively simple structure of collagen. Although there are already many steps inside the cell, procollagen is further processed after secretion. These steps are the C- and N-propeptide cleavages, cross linking and fibril formations. These steps are essential to transform procollagen to collagen, which is then capable of forming stable fibrils or other mature ECM structures.

Most cases of connective tissue disorders are caused by ECM protein deficiency. In many cases a genotype–phenotype correlation is difficult to establish from the observed phenotype of ECM molecules. The machinery proteins in the rER are potential candidates for these situations because defects in blueprints for the ECM molecules themselves and their folding machinery can affect the final structure and function. As we described, procollagens are biosynthesized in the rER requiring many proteins and steps to become functional. In this molecular ensemble, the lack of even one element may lead to aberrant molecules, which could result in diseases. This suggests that rER proteins are indirectly involved in the development and homeostasis of tissues. Characterization of procollagen biosynthesis and also ECM proteins inside the rER may provide new insight to understand the mechanism of the connective tissue disorders and offer new targets for drug development.

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